(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 January 2005 (06.01.2005)

PCT

(10) International Publication Number
WO 2005/000291 A1

(51) International Patent Classification[7]: A61K 31/335

(21) International Application Number:
PCT/US2004/020347

(22) International Filing Date: 28 June 2004 (28.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/483,335 27 June 2003 (27.06.2003) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/000291 A1

(54) Title: METHOD FOR TREATMENT OF IDIOPATHIC PULMONARY FIBROSIS USING TRIPTOLIDE DERIVATIVES

(57) Abstract: The use of immunosuppressive triptolide derivatives for the treatment of idiopathic pulmonary fibrosis (IPF) is described.

Method for Treatment of Idiopathic Pulmonary Fibrosis using Triptolide Derivatives

Field of the Invention

The invention is directed to treatment of Idiopathic Pulmonary Fibrosis (IPF), and in particular to use of triptolide derivatives to inhibit inflammation and/or fibrosis in patients afflicted with IPF.

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Background of the Invention

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with no known etiology. The disease occurs most often in adults between 50 and 70 years old, although children and infants can also be affected. IPF is characterized by excessive deposition of intracellular matrix and collagen in the lung interstitium and gradual replacement of the alveoli by scar tissue as a result of inflammation and fibrosis. Symptoms can include shortness of breath on exertion and, in later stages, at rest; decreased tolerance for activity; dry cough; chest pain; and harsh, rasping breath.

As the disease progresses, the increase in scar tissue interferes with the ability to transfer oxygen from the lungs to the bloodstream. Oxygen is given to patients who have low blood oxygen levels, and lung transplantation may be indicated in advanced cases. Most patients suffer from progressive disease despite treatment. Pulmonary hypertension and respiratory failure is the eventual outcome. The disease has a 5-year mortality rate of 50%.

The most potent profibrotic cytokine, TGF-β, induces collagen accumulation by several different mechanisms and plays a central role in the pathogenesis of IPF (Ignotz *et al.*, 1986; Raghow *et al.*, 1987; Raghu *et al.*, 1989; Crouch, 1990; Breen *et al.*, 1992; Coker *et al.*, 1998). Proinflammatory and profibrotic cytokine production is a major contributing factor to the accumulation of extracellular collagen in pulmonary fibrosis (McAnulty *et al.*, 1995).

Medications such as corticosteroids, such as prednisone, and cytotoxic drugs, such as cyclophosphamide, may be given to suppress inflammation. Corticosteroids are the mainstay of current drug therapy for IPF, but have limited efficacy and significant side effects.

Summary of the Invention

The invention provides, in one aspect, a method of inhibiting inflammation and/or fibrosis in a patient afflicted with idiopathic pulmonary fibrosis (IPF), comprising

administering to such a patient a triptolide derivative having immunosuppressive activity. In a related aspect, the invention is directed to the use of an immunosuppressive triptolide derivative for preparation of a medicament for inhibiting inflammation and fibrosis in a patient afflicted with idiopathic pulmonary fibrosis (IPF). Exemplary immunosuppressive triptolide derivatives are described below.

The triptolide compound may be employed in combination with an additional therapeutic agent selected from an antiviral agent, an antiinflammatory agent, such as a corticosteroid, an additional immunosuppressive agent, and an immune potentiator. Such agents are also described further below.

Detailed Description of the Invention

I. Triptolide Derivatives

In accordance with the present invention, triptolide derivatives having immunosuppressive activity are used to inhibit inflammation and fibrosis in a patient suffering from idiopathic pulmonary fibrosis (IPF).

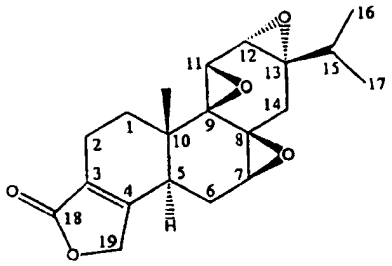
The compound triptolide, a diterpene triepoxide isolated from the Chinese medicinal plant *Tripterygium wilfordii*, has potent immunosuppressive and antiinflammatory properties. The compound has been shown to reduce T lymphocyte proliferation and recruitment (Qui *et al.*, 1999) and to suppress *in vitro* production of proinflammatory cytokines such as IFN-γ, TNF-α, IL-1β and IL-6, as shown in Table 1. To obtain the data, Jurkat cells were stimulated for 8 hr by PMA and ionomycin. Human peripheral blood mononuclear cells (PBMC) from a single donor were incubated for 24 hr with PHA. At the end of the culture period, each supernatant was harvested, and the cytokine content was assayed by ELISA.

Table 1. Suppression of cytokine production by triptolide

Cells and stimulus	Cytokine	IC_{50} (ng/ml)
PMA/ionomycin-induced Jurkat cells	IL-2	1.3
PHA-induced PBMC	IL-1β	0.45
	IL-2	0.38
	IL-6	1.5
	TNF-α	0.35
	IFN-γ	0.52

Triptolide suppresses the production of cytokines in a variety of *in vitro* systems. For example, triptolide inhibits early cytokine gene expression in Jurkat T cells, effectively suppressing T lymphocyte activation (Qui *et al.*, 1999). Triptolide inhibits production of IL-2 in activated human peripheral blood mononuclear cells (PBMC) and in activated Jurkat cells (Table 1; see Qui *et al.*, 1999, 2003). The secretion of the proinflammatory cytokines IFN-γ, TNF-α, IL-1β and IL-6 by PHA-activated human PBMC is also suppressed by triptolide (Table 1). Triptolide inhibits the expression of several cytokine genes in activated Jurkat cells, including IL-2, IL-3, IL-6, IL-8, IL-13, TNF-α, TGF-β, MIP-1α, MIP-1β, GM-CSF and RANTES (Qui *et al.*, 2003). In addition to its effects on immune cells, triptolide suppresses IL-8 expression by bronchial epithelial cells, inhibiting both IL-8 mRNA and IL-8 protein expression (Qui *et al.*, 1999).

For the purposes of the current disclosure, the following numbering scheme is used for triptolide derivatives:



With regard to structure, a "derivative" of triptolide preferably refers to a compound derived from triptolide via a modification which can include, for example: substitution of a hydrogen atom or hydroxyl group with hydroxyl, lower alkyl or alkenyl, lower acyl, lower alkoxy, lower alkyl amine, lower alkylthio, oxo (=O), or halogen; or conversion of a single bond to a double bond or to an epoxide. In this sense, "lower" preferably refers to C_1 to C_4; *e.g.* "lower alkyl" preferably refers to methyl, ethyl, or linear or branched propyl or butyl. Preferred hydrogen atom substitutions include hydroxyl, methyl, acetyl ($C(O)CH_3$) and fluoro.

Exemplary immunosuppressive triptolide derivatives for use in the invention include 14-methyltriptolide (designated PG670; see US application serial no. 10/738,753), 14-deoxy-14α-fluoro triptolide (designated PG763; see US application serial no. 10/786,663), 5-α-hydroxy triptolide (designated PG701; see U.S. application serial no. 60/532,702), 14-acetyl-5,6-didehydro triptolide (designated PG746; see U.S. application

serial no. 60/532,702), 19-methyl triptolide (designated PG795; see U.S. application serial no. 60/549,769), and 18-deoxo-19-dehydro-18-benzoyloxy-19-benzoyl triptolide (designated PG796; see U.S. application serial no. 60/549,769). Each of these compounds has demonstrated substantial immunosuppressive activity, as shown in the above-referenced patents and applications. For example, PG796 (18-deoxo-19-dehydro-18-benzoyloxy-19-benzoyl triptolide) showed a higher level of activity in a standard IL-2 inhibition assay than the known triptolide prodrug, triptolide 14-succinate. Both 5α-hydroxy triptolide (designated PG701) and 14-acetyl-5,6-didehydro triptolide (designated PG746) inhibited IL-2 production in Jurkat cells in a dose-dependent manner at concentrations of about 10 nM or greater, the latter after incubation for 16 hours with human serum. The activity of PG763 (14-deoxy-14α-fluoro triptolide) in assays evaluating cytotoxicity and IL-2 inhibition was nearly equivalent to that of native triptolide.

Methods of preparation of these and related compounds are described in the above-referenced applications, and several exemplary procedures are reproduced below in the Examples. Each of these US applications is hereby incorporated by reference in its entirety.

Any triptolide derivative having an ionizable group at physiological pH may be provided as a pharmaceutically acceptable salt. This term encompasses, for example, carboxylate salts having organic and inorganic cations, such as alkali and alkaline earth metal cations (for example, lithium, sodium, potassium, magnesium, barium and calcium); ammonium; or organic cations, for example, dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl) ammonium, phenylethylbenzylammonium, dibenzylethylenediammonium, and the like. Other suitable cations include the protonated forms of basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine, and arginine.

A triptolide derivative, as distinct from a triptolide prodrug, is not expected to undergo conversion to triptolide by a predictable mechanism. The derivatives noted above nonetheless exhibit biological activities shown by triptolide (e.g. cytotoxicity in human T cell lymphoma (Jurkat) cells and immunosuppressive activity, such as inhibition of IL-2), as reported, for example, in the US applications and patents cited above. (Note that while such derivatives could in fact be converted to triptolide *in vivo* by a yet unknown mechanism, they are not designed with such conversion in mind, as are triptolide

prodrugs.) This category may also include prodrugs of triptolide derivatives, e.g. an ester, carbamate or carbonate that undergoes conversion to the derivative *in vivo* via a predicable mechanism such as hydrolysis. Examples include 14-acetyl-5,6-didehydro triptolide and 18-deoxo-19-dehydro-18-benzoyloxy-19-benzoyl triptolide. In one embodiment, the derivative is a synthetic derivative. Derivatives may also include the naturally occurring compounds 16-hydroxytriptolide and tripdiolide (2-hydroxytriptolide).

Triptolide derivatives useful in the invention are not intended to be limited to the exemplary compounds discussed above. For examples of further derivatives, see the U.S. patents and applications cited above.

Derivatives with "immunosuppressive activity" can be identified via standard *in vitro* and *in vivo* assays. *In vitro* assays include the IL-2 inhibition assay described in co-owned PCT Pubn. No. WO 2003/101951; derivatives may also be tested for inhibition of TGF-β, using commercially available kits, such as the TGF-β Emax® ImmunoAssay System provided by Promega Corporation. Preferably, immunosuppressive activity is such that the target cytokine is inhibited by the derivative at a concentration at most 50 times greater, more preferably at most 10 times greater, and most preferably at most 5 times greater than the concentration of native triptolide that provides the same level of inhibition in the assay.

Derivatives may also be screened in *an vivo* animal model of IPF, such as the murine model of bleomycin-induced pulmonary fibrosis, described e.g. in Krishna *et al.*, 2001.

III. Treatment Methods

For administration to human patients, a reasonable range of doses is 0.1 to 40 μg/kg, depending upon the activity of the derivative compared to that of triptolide. While i.v. administration is preferred in a clinical setting, other modes of administration, such as parenteral or oral, may also be used, with higher dosages typically used for oral administration.

Liquid compositions can be prepared by dissolving or dispersing the triptolide compound (generally about 0.5% to about 20%) and optional pharmaceutical adjuvants in a pharmaceutically acceptable carrier, such as, for example, aqueous saline, aqueous dextrose, glycerol, or ethanol, to form a solution or suspension.

For use in oral liquid preparation, the composition may be prepared as a solution, suspension, emulsion, or syrup, being supplied either in liquid form or a dried form

suitable for hydration in water or normal saline. For i.v. or parenteral administration, of which the latter includes subcutaneous, intraperitoneal, or intramuscular injection, an injectable composition will typically contain the triptolide derivative in a suitable intravenous solution, such as sterile physiological salt solution.

The compound may also be administered by inhalation, in the form of aerosol particles, either solid or liquid, preferably of respirable size. Such particles are sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. In general, particles ranging from about 1 to 10 microns in size, and preferably less than about 5 microns in size, are respirable. Liquid compositions for inhalation comprise the active agent dispersed in an aqueous carrier, such as sterile pyrogen free saline solution or sterile pyrogen free water. If desired, the composition may be mixed with a propellant to assist in spraying the composition and forming an aerosol.

Formulations containing triptolide derivatives for use in the methods of the invention may take the form of solid, semi-solid, or lyophilized powder dosage forms, such as tablets, capsules, powders, or sustained-release formulations, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions typically include a conventional pharmaceutical carrier or excipient and may additionally include other medicinal agents, carriers, or adjuvants.

Preferably, the composition will be about 0.5% to 75% by weight of a triptolide derivative, with the remainder consisting of suitable pharmaceutical excipients. For oral administration, such excipients include pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. If desired, the composition may also contain minor amounts of non-toxic auxiliary substances such as wetting agents, emulsifying agents, or buffers.

Methods for preparing such dosage forms are known or will be apparent to those skilled in the art; for example, see Remington's Pharmaceutical Sciences (19th Ed., Williams & Wilkins, 1995). The composition to be administered will contain a quantity of the selected compound in an effective amount for inhibiting inflammation and fibrosis in an IPF patient as described herein.

V. Combination Treatment

Combination or multiple therapy is frequently indicated for IPF, as the symptoms of

the disease are treated rather than the initial cause of the disease. The triptolide derivatives may therefore be used in combination with other agents. These additional agents include, but are not limited to, antiviral agents, corticosteroids, additional immunosuppressive agents, *e.g.* as described above, and immune potentiators.

Other compounds with immunosuppressive activity include, for example: azathioprine, brequinar, chlorambucil, 2-chloro deoxyadenosine, cyclosporin, cyclophosphamide, 15-deoxyspergualin, dexamethasone, everolimus, fluorouracil, leflunomide, mercaptopurine, methotrexate, mitomycin, mitoxantrone, mizoribine (bredinin), mycophenolate mofetil, prednisone, prednisolone, sirolimus (rapamycin), thalidomide, tacrolimus (FK506), thioguanine, and thiopurine). Also included are cytokine antagonists comprised of soluble receptors, antibodies, or binding proteins for cytokines or cytokine receptors. Etanercept™ (a soluble TNF receptor antagonist), Infliximab™ (an anti-TNF antibody) and Anakinra™ (a soluble IL-1 receptor antagonist) are examples of cytokine antagonists, and reagents targeting these and other cytokines/cytokine receptors are in preclinical and clinical development.

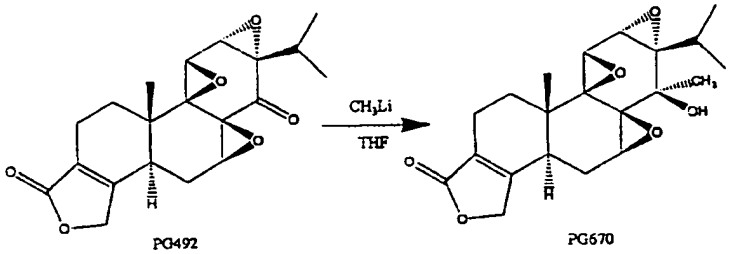
More than one of the cytokine antagonists described herein may be used in combination, since each cytokine antagonist is targeted at a single cytokine pathway. Combination treatment with triptolide compounds, immunosuppressive agents, and cytokine antagonists may be used to increase the effectiveness of the treatment.

As in any immunosuppressive therapy, it is advisable to monitor aspects of the immune system, to allow modulation of the treatment if necessary.

EXAMPLES

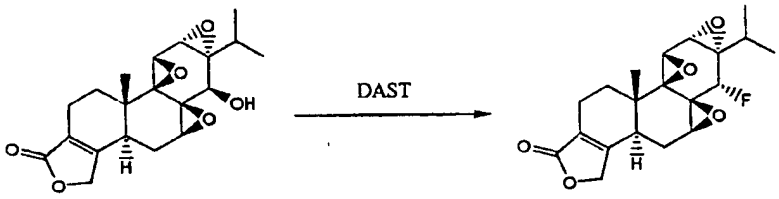
Methods of synthesis of various exemplary triptolide derivatives are provided below. All structures were verified by NMR.

Example 1. Preparation of 14-C-methyltriptolide (PG670)



To a solution of triptonide (designated PG492) (60 mg, 0.17 mmol) in THF (5 ml) at –78 °C was added 0.45 ml of methyl lithium (1.4 M solution in ethyl ether, 0.63 mmol, 3.7 eq) under N_2. The solution was stirred at –78 °C for 2 hrs 45 mins and then at room temperature for 2 hrs , at which time the starting material had disappeared on TLC. Acetic acid (1 ml) was slowly added. The solution was then concentrated under vacuum. The crude product was dissolved in dichloromethane (3 ml) and passed through a pad of silica gel, which was then washed with 5% methanol in ethyl acetate (80 ml). After removal of solvent, 78 mg of crude product was obtained. This was dissolved in acetonitrile (0.6 ml) and filtered. The product mixture was separated on HPLC, using a 10x250 mm column of Econosil C18 and a guard column cartridge (7.5x4.6 mm) of Alltima C18, both from Alltech, with mobile phase CH_3CN/H_2O 40/60 with a flow rate of 2.0 ml/min. The sixth peak, having a retention time of 32.13 mins, was collected and concentrated under vacuum. The product had m/z 374 (7.9 mg, yield: 12.6%).

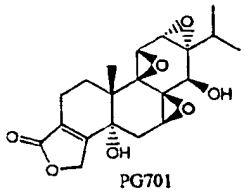
Example 2. Preparation of 14-deoxy-14α-fluoro triptolide



PG490 PG763

To a solution of PG490 (triptolide, 17.3 mg, 0.048 mmol) in dichloromethane (1.0 ml) at 0°C was added (diethylamino)sulfur trifluoride (DAST, 100 µl, 0.763 mmol) under N_2. The reaction mixture was stirred at 0°C for 2 hrs, and saturated $NaHCO_3$ solution (0.8 ml) was then added. The reaction mixture was extracted with 3 x 2 ml of dichloromethane. The combined organic layer was dried over anhydrous $NaSO_4$ and concentrated under vacuum. The product (PG763) was obtained in quantitative yield.

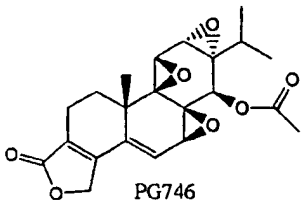
Example 3: Synthesis of 5-α-hydroxytriptolide (PG701)



PG701

To a solution of triptolide (437.6mg, 1.21mmol) in 1,4-dioxane (35mL) was added selenium dioxide (305.1mg, 2.75mmol). The reaction mixture was stirred at 90°C under N_2 for 70 hrs. After cooling to room temperature, the reaction mixture was filtered through Celite and concentrated under vacuum. The crude product was purified via preparative TLC (EtOAc/CH_2Cl2 3:7) to yield the desired product (211.7mg, 46.3%).

Example 4: Synthesis of 14-acetyl-5,6-didehydrotriptolide (PG746)

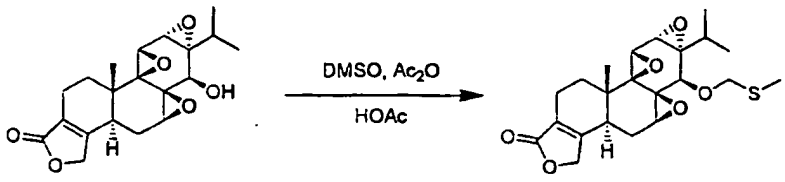


PG746

To a solution of 5-α-hydroxytriptolide (PG701, 98.3mg, 0.261mmol), 4-dimethylaminopyridine (DMAP, 45.2mg) and triethylamine (TEA, 0.50mL) in dichloromethane (5.0mL) was added acetic anhydride (0.247mL, 2.61mmol, 10.0eq) at room temperature under nitrogen. After stirring for 4-5 hrs at room temperature, methanol (1.0mL) was added, and the reaction mixture was concentrated under vacuum. The crude product, 14-acetyl-5-α-hydroxytriptolide, was purified using preparative TLC. To a solution of this material (10.5mg, 0.025mmol), in CH_2Cl_2 (0.50mL) at 0°C was added (diethylamino)sulfur trifluoride (DAST, 4.3 μL, 0.033mmol, 1.3eq). The reaction mixture was stirred at 0°C under N_2 for 40 mins. Saturated aq. $NaHCO_3$ (0.2mL) diluted with 0.3 mL H_2O was added to the reaction mixture at 0°C. The mixture was then extracted with dichloromethane (1.5, 2x2.0mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified using preparative TLC (EtOAc/hexanes/MeOH 40:60:5.0) to yield 4.0 mg product (39.8%).

Example 5. Preparation of 19-Methyl Triptolide (PG795)

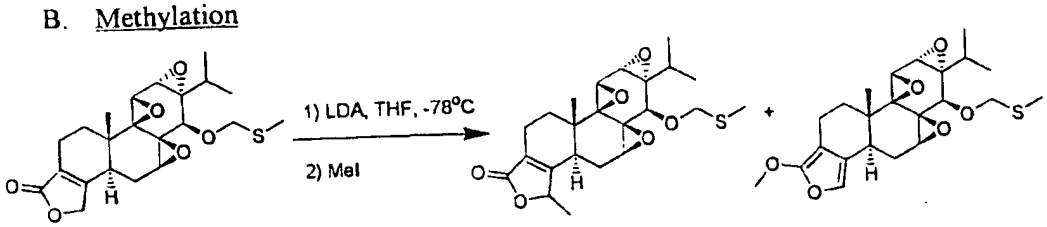
A. Protection of 14-hydroxyl group



PG691

To a solution of triptolide (0.56 g, 1.6 mmol) in DMSO (8.5 mL, 0.12 mol) was added acetic acid (28 mL, .49 mol) and acetic anhydride (5.6 mL, 59 mol), and the solution was stirred at room temperature for five days. The reaction mixture was poured into 200 mL of water and neutralized with solid $NaHCO_3$, added in portions. The mixture was extracted with ethyl acetate (150 mL x 3), and the extract was dried over anhydrous sodium sulfate. and concentrated to give an oil. Silica gel column chromatography purification (3:2 hexanes/EtOAc) gave the intermediate (PG691) (0.45 g, 69%) as a white foam.

B. Methylation

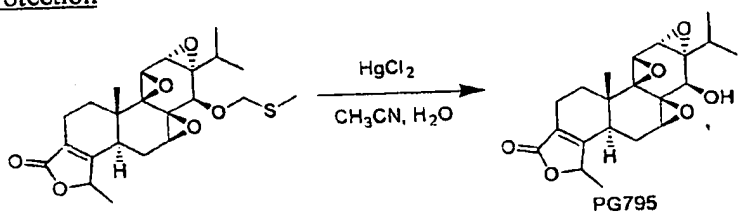


PG691

To a solution of PG691 (0.22g, 0.52 mmol) in anhydrous THF (10 mL) was added a solution of LDA in heptane/THF/ethyl benzene (0.30 mL of 2.0 M solution, 0.60 mmol) dropwise at –78 °C. The solution was stirred at this temperature for 15 min, followed by dropwise addition of CH_3I (50 µL, 0.80 mmol). The mixture was stirred at –78 °C for 2 h, then allowed to come to room temperature overnight.

The reaction mixture was neutralized with 1N HCl and extracted with EtOAc (10 mL x 3). The EtOAc solution was washed with 5% aqueous sodium thiosulfate (10 mL x 2) and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave an oil. Column purification (silica gel, 3:2 hexanes/EtOAc) gave two products, methylthiomethyl protected 19-methyltriptolide (45.9 mg, 20%) and methylthiomethyl protected 18-methoxyfuranotriptolide.

C. Deprotection



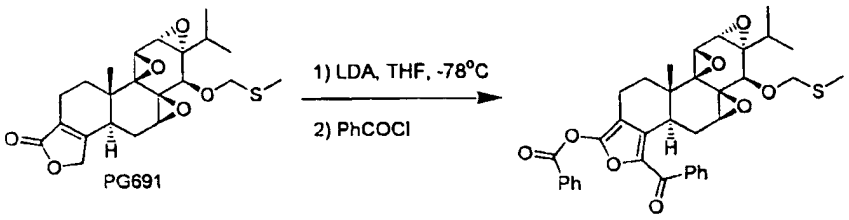
PG795

To a solution of methylthiomethyl protected 19-methyltriptolide, prepared as described above (45.9 mg, 0.106 mmol), in 1.5 mL acetonitrile/water (4:1) was added mercuric chloride (0.285 g, 1.05 mmol) in one portion. The resulting solution was stirred

at room temperature overnight. The white solid which precipitated from the solution was removed by filtration through Celite® and rinsed with ethyl acetate. The EtOAc solution was washed twice with 5% aqueous NH_4OAc. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product. Purification by column chromatography (silica gel, 1:1 hexanes/ethyl acetate) gave the product (39.5 mg, 99%).

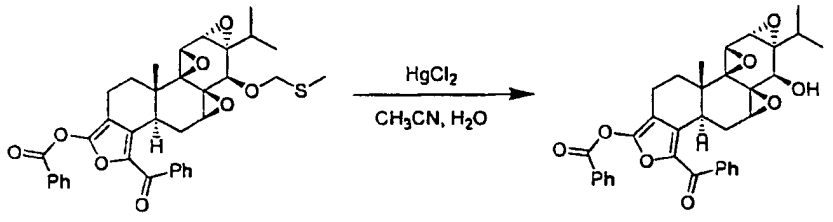
Example 6. Preparation of 18-deoxo-19-dehydro-18-benzoyloxy-19-benzoyl triptolide (PG796)

A. Acylation



To a solution of PG691, prepared as described above (73.1 mg, 0.174 mmol), in anhydrous THF (5 mL) was added a solution of LDA in heptane/THF/ethyl benzene (0.34 mmol) dropwise at –78 °C. The solution was stirred at this temperature for 15 min, followed by the dropwise addition of benzoyl chloride (100 μL, 0.86 mmol). The reaction was stirred at –78 °C for 2 h, then quenched with water and extracted with ethyl acetate (25 mL x 3). The combined organic solution was dried over anhydrous sodium sulfate. Concentration under reduced pressure gave an oil. Column purification (silica gel, 3:2 hexanes/ethyl acetate) gave the 14-protected product (51.2 mg, 47%).

B. Deprotection



To a solution of the 14-methylthiomethyl protected product, prepared as described above (51.2 mg, 0.0814 mmol), in 1.5 mL acetonitrile/water (4:1) was added mercuric chloride (0.22 g, 0.81 mmol) in one portion. The resulting solution was stirred at room temperature overnight. The white solid which precipitated from the solution was removed

by filtration through Celite® and rinsed with ethyl acetate. The EtOAc solution was washed twice with 5% aqueous NH_4OAc. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product. Purification by column chromatography provided the pure product (32.8 mg, 71%).

CLAIMS

1. A method of inhibiting inflammation and/or fibrosis in a patient suffering from idiopathic pulmonary fibrosis, comprising administering to such a patient a triptolide derivative having immunosuppressive activity.

2. The method of claim 1, wherein the immunosuppressive triptolide derivative is a compound derived from triptolide via substitution of a hydrogen atom with hydroxyl, lower alkyl, lower acyl, lower alkoxy, fluoro, or cyano.

3. The method of claim 1, wherein the immunosuppressive triptolide derivative is a compound derived from triptolide via replacement of a single bond with a double bond.

4. The method of claim 2, wherein said triptolide derivative is selected from the group consisting of 14-methyltriptolide, 14-deoxy-14α-fluoro triptolide, 5-α-hydroxy triptolide, 19-methyl triptolide, and 18-deoxo-19-dehydro-18-benzoyloxy-19-benzoyl triptolide.

5. . The method of claim 3, wherein said triptolide derivative is 14-acetyl-5,6-didehydro triptolide.

6. The method of claim 1, further comprising administering to said patient an additional therapeutic agent selected from an antiviral agent, an antiinflammatory agent, an additional immunosuppressive agent, and an immune potentiator.

7. Use of an immunosuppressive triptolide derivative compound for preparation of a medicament for inhibiting inflammation and/or fibrosis in a patient in a patient suffering from idiopathic pulmonary fibrosis.

8. The use of claim 7, wherein the immunosuppressive triptolide derivative is a compound derived from triptolide via substitution of a hydrogen atom with hydroxyl, lower alkyl, lower acyl, lower alkoxy, fluoro, or cyano.

9. The use of claim 7, wherein the immunosuppressive triptolide derivative is a

compound derived from triptolide via replacement of a single bond with a double bond.

10. The use of claim 8, wherein said triptolide derivative is selected from the group consisting of 14-methyltriptolide, 14-deoxy-14α-fluoro triptolide, 5-α-hydroxy triptolide, 19-methyl triptolide, and 18-deoxo-19-dehydro-18-benzoyloxy-19-benzoyl triptolide.

11. The use of claim 10, wherein said triptolide derivative is 14-acetyl-5,6-didehydro triptolide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/20347

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/335
US CL : 514/475

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/475

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,150,539 A (MUSSER) 21 November 2000(21.11.2000), see the entire document.	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search
29 October 2004 (29.10.2004)

Date of mailing of the international search report
17 NOV 2004

Name and mailing address of the ISA/US
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Form PCT/ISA/210 (second sheet) (July 1998)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 December 2003 (11.12.2003)

PCT

(10) International Publication Number
WO 2003/101951 A3

(51) International Patent Classification[7]: A61K 31/343, C07D 407/14

(21) International Application Number: PCT/US2003/017177

(22) International Filing Date: 29 May 2003 (29.05.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/384,480 31 May 2002 (31.05.2002) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 6 May 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/101951 A3

(54) Title: TRIPTOLIDE DERIVATIVES FOR MODULATION OF APOPTOSIS AND IMMUNOSUPPRESSION

(57) Abstract: Variously substituted carbonate and carbamate derivatives of triptolide compounds have good aqueous solubility and convert to biologically active compounds in vivo, at a rate which can be modulated by varying the substitution on the prodrug. The prodrugs are useful as immunosuppressive, anti-inflammatory and anticancer agents.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/17177

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/343; C07D 407/14
US CL : 514/468; 549/297

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/468; 549/297

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 6,569,893 B2 (DAI et al) 27 May 2003 (27.05.2003), see full text.	1-14

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Date of the actual completion of the international search	Date of mailing of the international search report
06 March 2004 (06.03.2004)	25 MAR 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Valerie Bell-Harris for Marianne Seidel Telephone No. 703-308-1123

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INTERNATIONAL SEARCH REPORT

PCT/US03/17177

Continuation of B. FIELDS SEARCHED Item 3:
USPATFUL, CAS ONLINE, REGISTRY, HCAPLUS,
structure searched and term searched:immunomodulator, autoimmune disorder, graft-versus-host disease, triptolide